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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/847,522	05/01/2001	Bradford W. Gibson	660088.434	4029

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SEED INTELLECTUAL PROPERTY LAW GROUP PLLC  
701 FIFTH AVE  
SUITE 6300  
SEATTLE, WA 98104-7092

EXAMINER
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COLE, MONIQUE T

ART UNIT	PAPER NUMBER
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1743

DATE MAILED: 03/24/2004

7

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/847,522

Applicant(s)

GIBSON ET AL.

Examiner

Monique T. Cole

Art Unit

1743

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 01 May 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-19 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 8-13 is/are allowed.
- 6) ☒ Claim(s) 1-5, 14-17 and 19 is/are rejected.
- 7) ☒ Claim(s) 6, 7 and 18 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948)                                    | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## DETAILED ACTION

### *Claim Rejections - 35 USC § 112*

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 16 & 17 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. In claim 17, the omitted steps are: taking a first mass spectrum of a protein fraction having at least one peptide that has a nitrotyrosine residue; selecting a candidate agent that may have the ability to reduce oxidative protein modification; contacting said candidate agent with the first mass spectrum; taking a second mass spectrum of the at least one peptide that has a nitrotyrosine residue after having been treated with the candidate agent. . . (steps as currently recited in the claim). The steps of claim 16 should be enumerated in much the same way. The recitation of the omitted steps serve solely as an example of what the Examiner feels is necessary to accurately describe the claimed method. Further clarification is required.

### *Claim Rejections - 35 USC § 102*

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1-4, 14, 15 & 19 are rejected under 35 U.S.C. 102(b) as being anticipated by *"Analytical Methods for 3-Nitrotyrosine as a Marker of Exposure to Reactive Nitrogen Species: A Review"* by Herce-Pagliai et al. (herein referred to as "Pagliai").

Pagliai teaches a method for determining oxidative modification of a protein that comprises analyzing the propensity of tyrosine residues in proteins to become oxidized upon contact with a reactive nitrogen species to form nitrotyrosine. Nitrotyrosine is taught as being a suitable marker for NO-mediated tissue damage and has been implicated in the development of some diseases associated with oxidative stress such as arteriosclerosis, rheumatoid arthritis, inflammation and neurodegenerative disorders.

On pages 332-333, Pagliai teaches that levels of nitrotyrosine in LDL were isolated from a person having a known disease associated with oxidative modification (arteriosclerosis) and compared against nitrotyrosine levels of a person known to be healthy in this regard. The quantitative method used to determine the nitrotyrosine levels was GC-MS. The article suggests that increasing levels of nitrotyrosine correlate to an increased incidence of diseases associated with oxidative stress, thus the fact that arteriosclerotic individual had 90-fold higher levels of nitrotyrosine as compared to the healthy individual confirmed the hypothesis of the article.

On page 334, Pagliai teaches that proteolytic agents such as trypsin may be used to generate a plurality of peptide fragments from a protein fraction to aid in the study the effects of nitrotyrosine on protein function.

*Claim Rejections - 35 USC § 103*

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pagliai as applied to claims 1-4, 14, 15 & 19 above, and further in view of "Peptide Sequencing by Mass Spectrometry for Homology Searches and Cloning of Genes" by Shevchenko et al. (herein referred to as "Shevchenko").

Pagliai, as applied above, fails to teach that the mass spectrometry analysis is generated by matrix assisted laser desorption ionization mass spectrometry (MALDI).

However, Shevchenko teaches that MALDI is employed as general strategy of high-throughput, unambiguous and sensitive mass spectrometric protein identification. This

Art Unit: 1743

technique has been found to be successful and conclusive in up to 90% of proteins & when the protein has been identified in this way no more analyses need to be performed. See pg. 483.

Thus, given the noted advantages of MALDI technique as taught in Shevchenko, it would have been obvious to one having ordinary skill in the art to modify the method of detection of nitrotyrosine residues in peptide fragments as disclosed in Pagliai to include performing MALDI analysis as a means to accurately and efficiently ascertain the presence of nitrotyrosine.

*Allowable Subject Matter*

6. Claims 6, 7, 18 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

7. Claims 8-13 are allowed.

8. Claims 16 & 17 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action.

9. The following is a statement of reasons for the indication of allowable subject matter: the prior art does not teach or reasonably suggest a method for identifying oxidative modification or determining protein tyrosine nitration in a subject wherein determination of nitrotyrosine comprises detection in the mass spectrum of a peptide comprising nitrotyrosine; a peptide comprising nitrotyrosine that lacks one oxygen atom and a peptide comprising nitrotyrosine that lacks two oxygen atoms. The prior art does not teach or reasonably suggest a method for identifying oxidative modification of a protein using mass spectrometry analysis wherein a peptide that includes a nitrotyrosine residue is converted to aminotyrosine, and wherein said conversion

Art Unit: 1743

indicates that the protein in the biological sample is oxidatively modified. The prior art does not teach or reasonably suggest a method for identifying oxidative modification in a protein comprising determining the protein from which said at least one peptide that includes a nitrotyrosine residue is derived and therefrom identifying a protein that is oxidatively modified in the disease. The prior art does not teach or reasonably suggest a method of identifying a suitable agent for treating a disease associated with oxidative modification of a protein wherein a candidate agent is selected upon a determination that it affects a decreased level of nitrotyrosine and reduces oxidative protein modification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Monique T. Cole whose telephone number is 571-272-1255. The examiner can normally be reached on Monday-Thursday from 6:30 A.M. to 4:00 P.M.

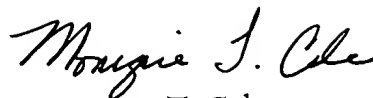
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on 571-272-1267. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Application/Control Number: 09/847,522

Art Unit: 1743

Page 7

A handwritten signature in cursive script, reading "Monique T. Cole".

Monique T. Cole

Examiner

Art Unit 1743

MC